PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness assessment of riluzole in the prevention of oxaliplatin-induced peripheral neuropathy – RILUZOX-01: protocol of a randomised, parallel, controlled, double-blind and multicentre study by the UNICANCER-AFSOS Supportive Care intergroup
AUTHORS	kerckhove, nicolas; Busserolles, Jérome; Stanbury, Trevor; Pereira, Bruno; Plence, Valérie; Bonnetain, Franck; Krakowski, Ivan; Eschalier, Alain; Pezet, Denis; Balayssac, David

VERSION 1 – REVIEW

REVIEWER	Jordi Bruna, MD, PhD Unit of Neuro-Oncology. Hospital Universitari de Bellvitge-ICO L'Hospitalet-Oncobell group., Spain
REVIEW RETURNED	26-Nov-2018

GENERAL COMMENTS	The trial planned by the authors is an interesting study about an unmet clinical need, like is the CIPN. Despite I think that the rationale is a little bit weak, because the pathophysiology of the oxaliplatin-induced peripheral neuropathy (OIPN) is only partially understood, I also think that it would be worthy to assess the role of riluzole in the oxaliplatin-induced peripheral neuropathy (OIPN), especially if the question is addressed using a placebo randomized trial with an adequate power and sample size, like is planned this trial. Unfortunately, these kinds of trials are very scarce in the CIPN field. For this reason, I sincerely congratulate the investigators for their efforts to address the question and achieve the funding to go ahead the study. However, I have some doubts or major queries about several questions regarding the current protocol. As the investigators know, OIPN is the oxaliplatin most prominent toxicity, both during and after the completion of chemotherapy. Two patterns of OIPN neurotoxicity are displayed: the acute form, characterised by cold triggered symptoms that occur immediately after infusion in most patients, and the cumulative neurotoxicity, resembling the classical cisplatin-induced peripheral neuropathy, characterised by distal paresthesias and numbness in the extremities, resulting in sensory ataxia and functional impairment. The impact on the oncologic treatment withdrawal and patient quality of life, and the physiopathology underlying to these two patterns are completely different. Moreover, the acute symptoms are usually transient and the chronic are long-lasting. In my opinion, the assessments of these two clinical pictures are not well delimited and defined in the protocol. According the rationale and background provided by the investigators, I can understand that riluzole can play a role preventing the acute neuropathic syndrome, but the evidence about its usefulness in the chronic is scarce, due to the glutamate

	has not been involved until now in the genesis of the chronic OIPN. But more important, the best tools to assess and adequately capture the acute and chronic disturbances are different, and the chronic OIPN is very dependent of the oxaliplatin total accumulated dose. The accumulated risk dose to develop chronic OPIN starts at the 6 cycle and usually it is not clinical relevant until the last treatment cycles or until finishing the chemo administration. Therefore, if the trial endpoint is the assessment after 6 cycles, the investigators probably can not assess the real impact of treatment in the chronic OIPN, the most fear adverse event related with the oxaliplatin administration. On the other hand, I also have doubts about the tools selected to measure the impact of treatment in the study endpoints. The investigators selected the CIPN20 to assess the primary objective, a patient reported outcome (PRO) instead a clinician reported outcome. It is true a lack of existing consensus about the best measure to use in these trials, and also the lack of precise correlation between the patient and clinician reported outcomes. Moreover, a phase 3 only can have 1 primary endpoint. CIPN20 has been used in another phase 3 trial as outcome measure for preventing OIPN. However, the clinimetric properties about the CIPN20 have raised doubts (Qual Life Res. 2017 Nov;26(11):2999-3010), and this measure is only accepted as a simple additive checklist results. Moreover, this questionnaire is neither a good tool to capture the transient symptoms related with the acute oxaliplatin-induced toxicity since it was designed to mainly assess the symptoms related with the chronic neuropathies. My recommendation regarding the above mentioned points should be change the time to assess the primary objective. Do the assessment after 12 cycles or at finishing the chemo treatment, if it happened before the 12th cycle. And regarding the tools, personally, I could prefer clinician reported outcomes like the TNS, but if the investigators prefer PROs, I would recommend the FACT, although its clinimetric properties has been less exhaustively assessed than CIPN20. Moreover, although not validated, I would also include some scales to assess the acute symptoms of the OIPN. Finally, another concerning major point with regard this trial is about the lack of specification to how manage the concomitant drugs that the patients can receive to control their pain, a frequent situation in colorectal patients, specially after the surgery. Some drugs could mask the OIPN-associated pain and the acute symptoms, and affect the trial outcome. If this kind of drugs prescription is not included as exclusion criteria, then it have to be well registered, balanced between arms or at least, the dosage required thorough the trial be constant. Other minor comments or questions are: 1. why do not include metastatic patients? This population can facilitate the recruitment, they also facilitate the assessment of safety and the potential interactions with the efficacy of the oncologic treatment, and also suffer the OIPN consequences. 2. I disagree with the scoring-correlation between the CIPN20 and the NCI-CTCAE, and the interpretation of this reference provided to justify it. 3. I think that it will be very difficult provide valuable data about disease free survival and overall survival if you only include non metastatic patients in the planned window trial time. 4. The criterion of a deterioration of 5 points in HRQoL requires a reference or will seem an arbitrary cutoff.

REVIEWER	Deng Bo China-Japan Friendship hospital
REVIEW RETURNED	24-Dec-2018

GENERAL COMMENTS	No scientific interesting. No basic treatment in placebo group. No electromyography test.

REVIEWER	Kathryn Ruddy Mayo Clinic
REVIEW RETURNED	22-Jan-2019

GENERAL COMMENTS	This paper describes an interesting study and will be of value to other investigators. It could be even better with some minor grammatical edits and the addition of the time points planned for the secondary endpoints. With regard to the grammatical edits, a few examples of minor necessary corrections include: 1) add "d" to "resolve" and "s" to "infusion" in the second sentence of the abstract; 2) add "s" to "cause" in the third sentence of the abstract; 3) change "reduce the effective clinical outcomes" to "impair clinical outcomes" in the fourth sentence of the abstract; 4) change "into" to "in" in the fifth sentence of the abstract.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Please leave your comments for the authors below The trial planned by the authors is an interesting study about an unmet clinical need, like is the CIPN. Despite I think that the rationale is a little bit weak, because the pathophysiology of the oxaliplatin-induced peripheral neuropathy (OIPN) is only partially understood, I also think that it would be worthy to assess the role of riluzole in the oxaliplatin-induced peripheral neuropathy (OIPN), especially if the question is addressed using a placebo randomized trial with an adequate power and sample size, like is planned this trial. Unfortunately, these kinds of trials are very scarce in the CIPN field. For this reason, I sincerely congratulate the investigators for their efforts to address the question and achieve the funding to go ahead the study. However, I have some doubts or major queries about several questions regarding the current protocol.

Q4 - As the investigators know, OIPN is the oxaliplatin most prominent toxicity, both during and after the completion of chemotherapy. Two patterns of OIPN neurotoxicity are displayed: the acute form, characterised by cold triggered symptoms that occur immediately after infusion in most patients, and the cumulative neurotoxicity, resembling the classical cisplatin-induced peripheral neuropathy, characterised by distal paresthesias and numbness in the extremities, resulting in sensory ataxia and functional impairment.
The impact on the oncologic treatment withdrawal and patient quality of life, and the physiopathology underlying to these two patterns are completely different. Moreover, the acute symptoms are usually transient and the chronic are long-lasting. In my opinion, the assessments of these two clinical pictures are not well delimited and defined in the protocol.

A4 - We agree with the reviewer regarding the acute and chronic aspects of OIPN. We have therefore modified our introduction accordingly.
Nevertheless, below, some details:
- This study aims to assess the preventive effect of riluzole on the OIPN on both acute and chronic aspects. Acute OIPN will be assessed with the monitoring of all neuropathic symptoms at each chemotherapy cycle by patients reports and by investigators with the NCI CTCAE and to a lesser extent by QLQ-CIPN20 during planned visits. The e-CRF plans to accurately report adverse events described by patients during each chemotherapy cycle. We agree that this will not be the most optimal way to evaluate acute neuropathy, but it remains, from a logistical point of view, the most appropriate way to reflect the real life of the investigator centres' functioning.
- The chronic OIPN will be assessed with the QLQ-CIPN20 and NCI CTCAE throughout the study: baseline, chemotherapy cycle 6, and 1-3-6-9-12 months after the last chemotherapy cycle.
- Neuropathic symptoms will not be assessed solely by QLQ-CIPN20. The CIPN20 score obtained will be associated with the NCI CTCAE grade, QLQ-C30 score, the frequency of adverse events and decrease / discontinuation of chemotherapy, as well as the possible use of pain medication for neuropathic pain relief. All these factors will be analysed and correlated with each other in order to evaluate as accurately as possible the effect of riluzole on these symptoms.

Q5 - According the rationale and background provided by the investigators, I can understand that riluzole can play a role preventing the acute neuropathic syndrome, but the evidence about its usefulness in the chronic is scarce, due to the glutamate has not been involved until now in the genesis of the chronic OIPN.

A5 - Regarding the acute form, oxaliplatin has been proposed to be a channelopathy inducer (Descoeur et al., 2011; Grolleau et al., 2001). Moreover, repeated oxaliplatin administration also leads to a massive increase of glutamate in the cerebrospinal fluid (Yamamoto et al., 2017). This is similar to the synaptic increase of glutamate that is known to occur in brain, spinal cord or retinal ischemia and that is found to be very deleterious for the neuronal cells (Benveniste et al., 1984; Choi and Rothman, 1990; Louzada-Junior et al., 1992; Nishizawa, 2001; Simpson et al., 1990). Riluzole is a dirty drug that has been shown to activate TREK and TRAAK channels and is also known to be an antiglutamate agent. Our recent publication (Poupon et al. Neuropharmacology 2018 PMID: 30056126) demonstrates the preventive effect of riluzole on OIPN development in mice. Riluzole partly or totally prevented both cephalic and extracephalic pain symptoms in oxaliplatin-treated animals. The analgesic efficacy of riluzole involves TREK-1 channel action at both locations. In addition, riluzole also prevented proprioceptive alterations observed in mice after repeated oxaliplatin injections. A neuroprotective effect of riluzole could account for its beneficial effect in oxaliplatin-treated animals, as suggested by the ultrastructural and electrophysiological results we obtained. Those results do not firmly involve glutamate. However, the neuroprotective effect of riluzole strongly support its potential usefulness in the chronic.

Q6 - But more important, the best tools to assess and adequately capture the acute and chronic disturbances are different, and the chronic OIPN is very dependent of the oxaliplatin total accumulated dose.

A6 - See A4 to Q4.
As the main objective is assessed at the end of the 6th cycle of chemotherapy and patients receiving at least 6 cycles of chemotherapy, the differences in oxaliplatin doses between patients will be minimal. Nevertheless, we agree that for secondary analysis at the end of chemotherapy, patients will have differences in terms of cumulative oxaliplatin doses and numbers of chemotherapy cycles. For this reason, as indicated in manuscript, the oxaliplatin total accumulated dose and cycle number will be reported and compared between the treatment groups.

Q7 - The accumulated risk dose to develop chronic OPIN starts at the 6 cycle and usually it is not clinical relevant until the last treatment cycles or until finishing the chemo administration. Therefore, if the trial endpoint is the assessment after 6 cycles, the investigators probably can not assess the real impact of treatment in the chronic OIPN, the most fear adverse event related with the oxaliplatin administration.

A7 - As indicated in previous comments, the study is not intended to assess acute or chronic neuropathy separately. The study aims to assess the incidence and severity of all OIPN symptoms (acute and chronic), depending on the preventive treatment received (placebo or riluzole).
Data on the kinetics of the appearance of chronic OIPN are scarce and non-homogeneous. We have based ourselves on the publication of Attal et al. 2009 (PMID: 19457614) which shows a neurological disturbance (cold hypersensitivity assessed with QST) close to the 6th cycle (considering significant disturbances in cycles 3 and 9). We therefore assume that a significant number of patients will have developed neuropathy at cycle 6.
We are aware that some patients develop OIPN at the end of chemotherapy (as described recently by Molassiotis et al. 2019, PMID: 30736741) and sometimes even after the end of chemotherapy cycles (coasting effect). Nevertheless, as indicated in the manuscript, this will be precisely assessed at the post-chemo follow-up (1-3-6-9 and 12 months after the last chemotherapy cycle) with, among others, the QLQ-CIPN20 questionnaire.

Q8 - On the other hand, I also have doubts about the tools selected to measure the impact of treatment in the study endpoints. The investigators selected the CIPN20 to assess the primary objective, a patient reported outcome (PRO) instead a clinician reported outcome. It is true a lack of existing consensus about the best measure to use in these trials, and also the lack of precise correlation between the patient and clinician reported outcomes. Moreover, a phase 3 only can have 1 primary endpoint. CIPN20 has been used in another phase 3 trial as outcome measure for preventing OIPN. However, the clinimetric properties about the CIPN20 have raised doubts (Qual Life Res. 2017 Nov;26(11):2999-3010), and this measure is only accepted as a simple additive checklist results. Moreover, this questionnaire is neither a good tool to capture the transient symptoms related with the acute oxaliplatin-induced toxicity since it was designed to mainly assess the symptoms related with the chronic neuropathies.

A8 - As above-mentioned, we agree for the acute OIPN because the assessment timing will be not adequate and is more reliable for the chronic OIPN, but the acute OIPN will be assessed at each chemotherapy cycle by patient and investigators with NCI CTCAE.
Moreover, indicated by “Trial designs for chemotherapy-induced peripheral neuropathy prevention: ACTTION recommendations” (PMID: 30054438) and in the publication of Kieffer et al. (Qual Life Res. 2017 PMID: 28634676), the QLQ-CIPN20 is also interesting by using the questionnaire at the individual item level to gain more insight into specific CIPN symptoms affecting individual patients or patient groups.

Q9 - My recommendation regarding the above mentioned points should be change the time to assess the primary objective. Do the assessment after 12 cycles or at finishing the chemo treatment, if it happened before the 12th cycle. And regarding the tools, personally, I could prefer clinician reported outcomes like the TNS, but if the investigators prefer PROs, I would recommend the FACT, although its clinimetric properties has been less exhaustively assessed than CIPN20. Moreover, although not validated, I would also include some scales to assess the acute symptoms of the OIPN.

A9 - We chose a PRO rather than a CRO because clinicians tend to underestimate the symptoms of CIPNs (Beutler et al. 2017, PMID: 28950347; Park et al. 2017, PMID: 29117336). In addition, a very recent article highlights the fact that PRO are preferable to CRO and that the QLQ-CIPN20 questionnaire is the most appropriate way to evaluate CIPN (Dorsey et al. 2019,

https://doi.org/10.1093/jnci/djz011) Page 12/53: “A 2016 review paper outlined the results and lessons learned from 15 recent NCI-funded trials testing pharmacologic agents for the prevention or treatment of CIPN (Majithia et al. 2016, PMID: 26686859) and a recent paper provided recommendations for CIPN trial design (Gewandter et al. 2018, PMID: 30054438). The lessons learned included: the fact that early studies were underpowered, that patient-reported symptoms of CIPN are more sensitive outcomes than clinician-based assessments of CIPN…”; Page 16/53: “We recommend the CIPN-20 as one measure of phenotype specificity” and Table 2 Page 52/53 “Future studies should consider use of the patient-reported CIPN-20 questionnaire”.

Similarly, some clinicians do not have the tools or are not sufficiently familiar with CIPN to properly evaluate OIPN using CROs. This partly explains the underestimation of symptoms. Therefore, in addition to simplifying the logistics of the trial and being as close as possible to the actual conditions of french medical care, we have chosen to use a PRO to assess the symptoms of OIPN. Finally, the ACTTION consortium mentions that there is insufficient evidence to recommend one against the other (FACT vs QLQ-CIPN20; PMID: 30054438), and that FACT and CIPN20 appear similar (PMID: 29873180).
In order to better argue the choice of the CIPN20 as an evaluation criterion, we have added these various clarifications in the article.

Q10 - Finally, another concerning major point with regard this trial is about the lack of specification to how manage the concomitant drugs that the patients can receive to control their pain, a frequent situation in colorectal patients, specially after the surgery. Some drugs could mask the OIPN-associated pain and the acute symptoms, and affect the trial outcome. If this kind of drugs prescription is not included as exclusion criteria, then it have to be well registered, balanced between arms or at least, the dosage required thorough the trial be constant.

A10 - We did not want to change the practice of the associated centres and remain close to actual medical care conditions, and especially for ethical reasons (pain management). Nevertheless, we are aware of this probable bias and to best control it, all analgesics used by patients will be recorded throughout the study and compared between treatment groups.

Other minor comments or questions are:
Q11 - why do not include metastatic patients? This population can facilitate the recruitment, they also facilitate the assessment of safety and the potential interactions with the efficacy of the oncologic treatment, and also suffer the OIPN consequences.

A11 - Metastatic patients will not be included due to the heterogeneity of this population (number and location of metastases, different types of previous chemotherapy, painful condition and limited survival).

Q12 - I disagree with the scoring-correlation between the CIPN20 and the NCI-CTCAE, and the interpretation of this reference provided to justify it.

A12 - The publication of Alberti et al. (Ann Oncol 2013) shown a high relation between QLQ-CIPN20 scores and NCI-CTCAE sensory grade ($p<0.001$), and a less clear relation was noted for TNSc models. Moreover, the QLQ-CPIN20 scoring was able to discriminate NCI-CTCAE grade 1 versus grade 2 ($p<0.001$), and grade 2 versus grade 3/4 ($p<0.001$). However, the QLQ-CIPN20 scoring was not able to discriminate grade 0 versus grade 1 ($p=0.53$).
QLQ-CIPN20 scores between 30 and 40 (median ≈ 35, IQR ≈ [26;50] and mean ≈ 39) were associated to a NCI-CTCAE sensory grade 2.
QLQ-CIPN20 scores >40 (median ≈ 59, IQR ≈ [39;62] and mean ≈ 57) were associated to a NCI-CTCAE sensory grade 3/4.

The scores of the QLQ-CIPN20 (global scores and each dimension sensory, motor and vegetative) will be used as a quantitative variable (0-100) and the sensory dimension of the QLQ-CIPN20 will be used also as a qualitative variable to extrapolate the grade of OIPN.
In order to respond to the reviewer's remark, we have revised our grade cut-offs to make them more consistent. In this way, we propose the following cut-off values of the QLQ-CIPN20 sensory dimension: scores <30 for grade 0/1, scores 30-40 for grade 2 and scores >40 for grade 3/4. The protocol has been modified according to these cut-offs.

Q13 -I think that it will be very difficult provide valuable data about disease free survival and overall survival if you only include non metastatic patients in the planned window trial time.

A13 - We fully agree, but it is necessary to ensure the short-term effect of riluzole on cancer progression and the efficacy of oxaliplatin, even though in vitro and in vivo animal data do not demonstrate any deleterious effect of riluzole on the anticancer efficacy of oxaliplatin.

Q14 - The criterion of a deterioration of 5 points in HRQoL requires a reference or will seem an arbitrary cutoff.

A14 - HRQoL will be evaluated using the QLQ-C30 at baseline and at each planned visit until the end of the study or death. Functional scale, symptom scale, global health status, and financial difficulties were analyzed in QLQ-C30. The time of deterioration was defined as the time interval between randomization and the first decrease in HRQoL score ≥ 5-point with no further improvement in HRQoL score ≥ 5 points or any further HRQoL data. (Hamidou et al. 2016 (PMID: 27310205).
This has been added in manuscript.

Reviewer: 2
Please leave your comments for the authors below
Q15 - No scientific interesting. No basic treatment in placebo group. No electromyography test.

A15 - We are surprised by this very short revision and these comments, we consider that this study is of great scientific interest for the following reasons:
- CIPN are a very frequent and problematic adverse event induced by neurotoxic anti-cancer drugs
- No preventive or curative treatment. Only dose reduction or stop chemotherapy, without currently having any studies assessing its impact on patient survival and the efficacy of chemotherapy.
- 30% of patients develop chronic neuropathy
- Quality of life of patients severely degraded during and after chemotherapy
- Oncologist's helplessness in the presence of this adverse event
Concerning the basic treatment in placebo group, we remind the reviewer that there are no drugs with equivocal preventive or curative efficacy on CIPN, and even duloxetine, which is the treatment that appears to have a therapeutic effect in the treatment of CIPN, has not been evaluated in the prevention of CIPN, so there is no gold standard for CIPN prevention (Hershman et al. 2014, PMID: 24733808; Kerckhove et al. 2017, PMID: 28286483).
Concerning the scientific interest of the use of riluzole for the prevention of OIPN, we invite the reviewer to read the recent bibliography on this subject: Answer A5 to Q5.
Finally, electromyographic analyses are certainly interesting but complicated to implement and expensive in a multicentre trial, and remain quite far from our clinical practice.

Reviewer: 3
Q16 - Please leave your comments for the authors below This paper describes an interesting study and will be of value to other investigators. It could be even better with some minor grammatical edits and the addition of the time points planned for the secondary endpoints. With regard to the grammatical edits, a few examples of minor necessary corrections include: 1) add "d" to "resolve" and

"s" to "infusion" in the second sentence of the abstract; 2) add "s" to "cause" in the third sentence of the abstract; 3) change "reduce the effective clinical outcomes" to "impair clinical outcomes" in the fourth sentence of the abstract; 4) change "into" to "in" in the fifth sentence of the abstract.

A16 - The corrections have been made.
The timeline for interventions is described in the text, but for a better understanding, this has been added to Figure 1.